PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P 21059		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/19497	14/07/2000	13/07/1999
International Patent Classification (IPC) or national classification and IPC G01N33/50		
Applicant AMYLIN PHARMACEUTICALS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/02/2001	30.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giry, M Telephone No. +49 89 2399 7328

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/19497

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-29,31,32	as originally filed	
30	with telefax of	18/10/2001

Claims, No.:

1-19	with telefax of	18/10/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7, 9, 11, 13-19
	No:	Claims	1-6, 8, 10, 12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 - **Reference** is made to the following documents :

D1: K. Miller et al. : 'Membrane-bound and solubilized brain $5HT_3$ receptors: improved radioligand binding assays using bovine area postrema or rat cortex and the radioligands ^{3}H-GR65630, ^{3}H-BRL43694, and ^{3}H-LY278584.' Synapse, vol. 11, no. 1, 1992, pages 58-66

D2: B. A. Whelan et al. : 'Synthesis and structural, conformational, biochemical, and pharmacological study of new compounds derived from Tropane-3-spiro 4'(5')-imidazoline as potential 5-HT_3 receptor antagonists' J. Pharm. Sci., vol. 84, no. 1, January 1995, pages 101-106

D3: US-A-5 264 372, 23 November 1993, cited in the application

2 - **Novelty** - Art. 33(1) and (2) PCT :

2.1 Document D1 concerns the study of serotonine (5HT) receptors in bovine *area postrema* tissue. Document D1 discloses radioligands binding assays using bovine *area postrema* homogenates and the $5HT_3$ receptor antagonists ^{3}H-GR65630 and ^{3}H-BRL43694 in competition experiments (p. 59, col. 2, § "Radioligand binding studies of membrane-bound $5HT_3$ receptors") and presents representative competition curves for antagonists and agonists competed for specific ^{3}H-GR65630 or ^{3}H-BRL43694 binding (p. 61, Figures 5 and 6 ; p.62, Table II). Document D1 therefore appears to be novelty destroying for the subject-matter of claims 1-6, 8, 10 and 12.

2.2 Document D2 describes the synthesis of compounds 5(6)a-f derived from tropane-3-spiro-4'-imidazoline and the effects of said compounds on the binding of ^{3}H-GR65630 to brain *area postrema* membranes in competition experiments (p. 103, col. 2, 3 last lines to p. 104, col. 2, line 18 ; Figures 4 and 5 ; p. 105, col. 2, lines 37-65). Thus, in light of document D2, the subject-matter of claims 1-6, 8, 10 and 12 cannot be regarded as novel.

2.3 The available prior art documents disclose neither an assay method according to claims 7 and 9, a method for separating *area postrema* binding compounds wherein components of said *area postrema* are bound to a solid carrier (claim 12), nor a method of screening for a compound able to modulate a "biological function of the *area postrema* related to fuel homeostasis" (claims 14-20). Consequently, the subject-matter of claims 7, 9, 11 and 13-19 can be considered as new.

3 - **Inventive step** - Art. 33(1) and (3) PCT :

3.1 The two steps subject-matter of dependent claims 7 and 9 that further characterize the known methods of claims 1 and 2, respectively, fall within the customary practice followed by one skilled in the art. Thus, the subject-matter of claims 7 and 9 cannot be regarded as involving an inventive step.

3.2 Document D3 which is considered to represent the closest prior art document discloses methods for identifying or screening or characterizing or assaying or isolating known or candidates agonists and antagonists of amylin comprising binding assays utilizing preparations containing specific receptors for amylin. Membranes from the brain that contain high density receptors for amylin are used in the methods of the invention and as a source of amylin receptors (Abstract). The subject-matter of the present application differs from document D3 in that it concerns screening, identifying, characterizing, assaying and isolating candidate agonists and antagonists of different compounds. The problem to be solved by the present application can therefore be seen in providing screening, identifying, characterizing, assaying and isolating candidate agonists and antagonists of alternative compounds.

3.3 Document D3 discloses that the basal forebrain tissue is used as an amylin receptor preparation and may be bound to a solid phase and used in various affinity chromatography methods, for example for the purification of amylin or the evaluation of samples known or suspected to contain amylin, amylin agonists or amylin antagonists (col. 6, lines 52-57 ; col. 14, line 60 to col. 15, line 26). The selection of *area postrema* preparations as a source of receptors would be obvious to the skilled person since it appears to be well-known in the art that the

area postrema is a hindbrain region enriched in various receptors for peptides hormones (see p. 2, lines 22-28 of the description). The selection of this particular tissue does not appear to be linked to any unexpected effects. Therefore, the subject-matter of independent claim 11 cannot be considered as involving an inventive step.

3.4 Independent claim 13 concerns a method of screening for a "compound able to modulate a biological function of the *area postrema* related to fuel homeostasis" comprising adding a compound to said tissue preparation and measuring the effect of the compound on said biological function. Such methods comprising these two steps are customary in the field. Furthermore, it appears to be well-known in the art that receptors for hormones involved in this mechanism such as insulin, vasopressin, amylin, are located in this area of the brain (see p. 2, lines 22-28 of the description) and document D1 reports that $5HT_3$ receptor antagonists are effective antiemetic drug, especially useful in reversing the gastrointestinal disturbances (p. 58, col. 1, lines 8-11). Therefore, it appears that selecting *area postrema* to conduct the method in relation to a biological function related to fuel homeostasis would be obvious to one skilled in the art. Hence, the subject-matter of claim 13 cannot be considered as involving an inventive step.

3.5 In light of documents D1 and D3 teaching that amylin is a hormone isolated from pancreas and is associated with diabetes, claims 14-19 dependent on claim 13 do not appear to contain any additional technical feature which in combination with the features of the claim to which they refer can be regarded as involving an inventive step.

Re Item VIII

Certain observations on the international application

1. The application now comprises two claims numbered "claim 14" and no "claim 13". Therefore, the first claim 14 has been considered as claim 13.

2. The Applicant's attention is drawn to the fact that features mentioned after "optionally" in claims 10 and 12 are regarded as optional features which have no limiting effects on the claims (Art. 6 PCT).

3. Since the method of claim 10 appears to be achieved by the same steps as those necessary to perform the method of claim 6, it appears that claim 10 is superfluous and should have been deleted (Art. 6 PCT).